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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,464	10/18/2001	William D. Huse	AME-06381	7635

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/982,464	HUSE ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,7,9,13,15,19,21 and 25-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,7,9,13,15,19,21 and 25-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/19/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 19 August 2005 has been entered.

2. Claims 2, 4-6, 8, 10-12, 14, 16-18, 20 and 22-24 are cancelled.

Claims 1, 3, 7, 9, 13, 15, 19 and 21 have been amended.

Claims 25-42 have been added.

3. Claims 1, 3, 7, 9, 13, 15, 19, 21 and 25-42 are under examination.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Rejections.

Withdrawn Rejections

6. The rejections of claims 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 in the previous Office Action mailed 2/25/2005 are withdrawn in view of the cancellation of the claims.

Response to Arguments

7. The rejection of claims 1, 3, 7, 9, 13, 15, 19, 21 and applied to newly added claims 25-45 under 35 U.S.C 103(a) as being unpatentable over Jones et al (Nature

321:522, 1986) in view of Yelton et al (The Journal of Immunology 155:1994-2004, 1995) and Soderlind et al (Gene 160:269-272, 1995) and Hagiwara et al US Patent 5,589,573, issued 12/96) is maintained.

The response filed 8/19/2005 has been fully considered, but is deemed not to be persuasive. The response argues that there is no motivation to combine the references cited by the examiner and one of the references actually suggests that the presently claimed method is not likely to work. In response, this argument appears to go more towards enablement of the presently claimed method, however, Applicant is reminded that obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). With respect to the lack of motivation, Applicant argues that Yelton teaches affinity maturation by modifying the CDRs in the context of an antibody, which comprises its original CDRs and there was no motivation to modify the CDRs once they had been grafted into a different framework. Additionally, Applicant argues Yelton, quoting the last paragraph of the first column at page 2002 and stating that there may be no clear advantage of affinity maturing an antibody to improve therapeutic potential. Applicant argues Soderlind stating that Soderlind teaches modifying CDRs in the context of an original framework and not as presently claimed wherein non-human CDRs are grafted onto an unmodified human framework. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there

must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, Jones et al teach CDR grafting using unmodified human framework regions and the humanized and parental antibody had similar affinities for either hapten (NP-cap and NIP-cap) and Yelton teach that CDR targeted mutagenesis can yield higher affinity antibodies that have an improved targeting and better localization of therapeutic agents at the target site (see page 2002, right column) and according to Yelton "It is now possible to change the form, affinity, and potentially the specificity of Abs to optimize them for delivering a wide variety of therapeutic agents to tumor cells." (page 2002, last sentence of right column) and Soderlind teaches libraries of variable domains wherein the CDRs are mutagenized and the frameworks were unchanged and the libraries were made by overlapping oligos, which allow the construction of the library in one single PCR reaction. Thus, there would be an advantage to using overlapping oligos for mutating the CDRs according to Yelton et al in the method of CDR grafting as taught by Jones for antibody optimization. Applicant is reminded that the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of

reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983) (MPEP 2144). Further, one of ordinary skill in the art would have had a reasonable expectation of success in making the above modification because Jones teaches the CDR grafted antibody had similar affinity for either hapten and Yelton produced two antibody mutants with higher affinity, and improved targeting and localization. Additionally, with respect to Applicant's arguments against the specific teachings of Yelton and Soderlind, Applicant is reminded that references are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures (In re Bozek, 163 USPQ 545 (CCPA 1969)) and one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Applicant also argues that the present invention is nonobvious in view that the art taught away from modifying only the donor CDRs when grafted into a human acceptor framework, citing Queen et al, Reichmann et al and Co et al for support. In response to this argument, the art of Queen et al, Reichmann et al and Co et al were not cited in the present rejection and are not relevant.

8. The rejection of claims 1, 3, 7, 9, 13, 15, 19, 21 and applied to newly added claims 25-45 under 35 U.S.C 103(a) as being unpatentable over Jones et al (Nature 321:522, 1986) in view of Wu et al (PNAS 95:6037-6042, 5/98) and Soderlind et al (Gene 160:269-272, 1995) and Hagiwara et al US Patent 5,589,573, issued 12/96) is maintained.

The response filed 8/19/2005 has been fully considered, but is deemed not to be persuasive. The response argues that the state of the art as evidenced by Reichmann et al and Queen et al was to modify the human frameworks after grafting donor mouse CDRs into such a framework. Again, the art of Reichmann et al and Queen et al were not cited in the instant rejection. Applicant argues the specific teachings of Soderlind, stating that Soderlind teaches modifying CDRs in the context of an original framework and not as presently claimed wherein non-human CDRs are grafted onto an unmodified human framework and there would be no motivation to combine Soderlind with the teachings of Wu et al and Jones et al. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art,

rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, Jones et al teach CDR grafting using unmodified human framework regions and the humanized and parental antibody had similar affinities for either hapten (NP-cap and NIP-cap) and Wu teach a CDR targeted mutagenesis strategy wherein the frameworks were unchanged, which resulted in improved antibody affinity and Soderlind teaches libraries of variable domains wherein the CDRs are mutagenized and the frameworks were unchanged and the libraries were made by overlapping oligos, which allow the construction of the library in one single PCR reaction. Thus, there would be an advantage to using overlapping oligos of for antibody affinity maturation in the method of CDR grafting. Applicant is reminded that the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983) (MPEP 2144). With respect to Applicant's arguments against the specific teachings of Yelton and Soderlind, Applicant is reminded that references are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures (In re Bozek, 163 USPQ 545 (CCPA 1969)) and one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Therefore, the invention as a whole was prima facie obvious to one of ordinary

skill in the art at the time the invention was made, as evidenced by the references.

New Grounds of Rejections

9. Claims 41-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 41-45 are indefinite in the recitation "to produce an antibody variable region comprising unmodified heavy chain and light chain frameworks..." in part C of claim 41. It is unclear what is meant by coexpressing the heavy chain variable regions with the light chain variable regions to produce an antibody variable region since both the heavy chain variable region and the light chain variable region are each variable regions and coexpression of the two would produce an antibody and not a single antibody variable region. Further, the preamble of claim 41 appears to be drawn to a method of producing antibody variable regions, however, the active method steps of the claim appear to produce an antibody comprising a heavy chain variable region and a light chain variable region. Is the method directed towards producing a library (i.e. population) of altered antibodies or just altered variable regions? As written, one skilled in the art would not be reasonably apprised of the metes and bounds of the claims .

b. Claims 42-45 are indefinite for reciting "said antibody variable region". There is insufficient antecedent basis for this limitation. Is the phrase "said antibody variable region" referring to the heavy chain variable region(s) or the light chain variable region(s)?

c. Claims 43-45 are indefinite for reciting said antibody variable region further comprising at least four, at least five and at least six modified complementarity-determining regions, respectively. It is unclear what is contemplated by the claims because an antibody variable region only comprises three complementarity-determining regions, each flanked by a framework region.

10. Claims 1, 3, 7, 9, 13, 15, 19, 21 and 25-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of constructing an antibody comprising an altered heavy chain variable region and/or an altered light chain variable region comprising the recited method steps, wherein the antibody comprises all six CDRs, three from the heavy chain and three from the light chain and binds antigen, does not reasonably provide enablement for a method of constructing an altered heavy chain variable region and/or an altered light chain variable region comprising the recited method steps, wherein the variable regions comprise at least a portion of a CDR and does not comprise all six CDRs, three from the heavy chain and three from the light chain and does not bind antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence

or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly dawn to heavy and light chain variable regions comprising at least a portion of a CDR and do not bind antigen. Thus, the claims encompass fragments of an antibody that do not contain a full set of 6 CDRs, and do not bind antigen.

The specification discloses only antibodies comprising heavy chain variable regions that comprise CDR1, CDR2 and CDR3 and light chain variable regions that comprise CDR1, CDR2 and CDR3 and the antibody binds antigen (i.e., CD40) (see Example). The specification does not disclose heavy chain variable regions comprising at least a portion of a CDR or light chain variable regions comprising at least a portion of a CDR, wherein the heavy chain or light chain binds antigen.

It is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light

chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol. 79: page 1979). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that the heavy and light chain variable regions comprising a portion of a CDR as defined by the claims, which contain less than the full complement of CDRs from the heavy and light chain variable regions have the required binding function. Further, although claims 3, 9, 15, 21, 27-28, 31-32, 35-36 and 39-40 require the coexpression of the complementary heavy or light chain respectively, the claims still encompass portions of a CDR, which contain less than the full complement of CDRs from the heavy and light chain variable regions and would not have the required binding function. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of using the recited antibody fragments containing fewer than 6 CDRs, resulting in an antibody that retains the antigen binding function of the parental antibody. One of skill in the art would neither expect nor predict the appropriate functioning of the altered heavy and light chain variable regions as broadly as is claimed.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to altered heavy chain variable regions and/or light chain variable regions comprising a portion of a CDR, wherein the altered heavy and/or light chain variable regions do not bind antigen. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

11. Claims 1, 3, 7, 9, 13, 15, 19, 21, and 25-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicant broadly claims a method for constructing populations of altered heavy chain variable regions and/or altered light chain variable regions comprising unmodified human framework regions. The written description in this instant case has not been sufficiently set forth. Applicants specification discloses methods, which combine CDR grafting and affinity reacquisition of the grafted variable region into a single step, wherein the method comprises constructing a population of altered antibody variable regions of an antibody containing acceptor framework regions containing a plurality of different amino acids at one or more acceptor framework region amino acid positions and donor CDRs containing a plurality of different amino acids at one or more donor

CDR amino acid positions (see pages 3 and 5-6 of the specification). The disclosure only provides a single working example of the disclosed method, which comprises humanization of a CD40 antibody and combines CDR grafting with the identification and substitution of select amino acid positions in the human acceptor frameworks (see pages 46-62 of the specification). Therefore the written description is not commensurate in scope with the claims broadly drawn to a method for constructing populations of altered heavy chain variable regions and/or altered light chain variable regions comprising unmodified human framework regions and at least a portion of a donor CDR, which according to Applicant's disclosure, CDR grafting alone is imperfect because CDR grafting often diminishes the binding activity of the resulting humanized antibody (page 2 of the specification). Further, applicant has not reduced to practice the presently claimed method drawn to CDR grafting into unmodified human acceptor frameworks. Accordingly, the disclosed structural elements, which distinguish the presently claimed invention are limited to CDR grafting combined with affinity reacquisition comprising amino acid substitutions at select positions in the human acceptor framework regions.

Conception does not occur unless one has a mental picture of the structure of the molecule, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description'

inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

As discussed above, there is insufficient written description to support the presently claimed method as provided by the Written Description Guidelines published

in the January 5, 2001 Federal Register at Volume 66, Number 4, pages 1099-1111. Applicant is referred to the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph.

Conclusions

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER